beta-Blockers May Reduce Mortality and Risk of Exacerbations in Patients With Chronic Obstructive Pulmonary Disease

Rutten, Frans H.; Zuithoff, Nicolaas P. A.; Hak, Eelko; Grobbee, Diederick E.; Hoes, Arno W.

Published in:
Archives of Internal Medicine

Publication date:
2010

β-Blockers May Reduce Mortality and Risk of Exacerbations in Patients With Chronic Obstructive Pulmonary Disease

Frans H. Rutten, MD, PhD; Nicolaas P. A. Zuithoff, MSc; Eelko Hak, MSc, PhD; Diederick E. Grobbee, MD, PhD; Arno W. Hoes, MD, PhD

Background: Physicians avoid the use of β-blockers in patients with chronic obstructive pulmonary disease (COPD) and concurrent cardiovascular disease because of concerns about adverse pulmonary effects. We assessed the long-term effect of β-blocker use on survival and exacerbations in patients with COPD.

Methods: An observational cohort study using data from the electronic medical records of 23 general practices in the Netherlands. The data included standardized information about daily patient contacts, diagnoses, and drug prescriptions.

Results: In total, the study included 2230 patients 45 years and older with an incident or prevalent diagnosis of COPD between 1996 and 2006. The mean (SD) age of the patients with COPD was 64.8 (11.2) years at the start of the study, and 53% of the patients were male. During a mean (SD) follow-up of 7.2 (2.8) years, 686 patients (30.8%) died and 1055 (47.3%) had at least 1 exacerbation of COPD. The crude and adjusted hazard ratios with Cox regression analysis of β-blocker use for mortality were 0.70 (95% confidence interval [CI], 0.59-0.84) and 0.68 (95% CI, 0.56-0.83), respectively. The crude and adjusted hazard ratios for exacerbation of COPD were 0.73 (95% CI, 0.63-0.83) and 0.71 (95% CI, 0.60-0.83), respectively. The adjusted hazard ratios with the propensity score methods were even lower. Subgroup analyses revealed that patients with COPD but without overt cardiovascular disease had similar results.

Conclusion: Treatment with β-blockers may reduce the risk of exacerbations and improve survival in patients with COPD, possibly as a result of dual cardiopulmonary protective properties.

Arch Intern Med. 2010;170(10):880-887

CHRONIC OBSTRUCTIVE PULMONARY disease (COPD) is a common disease with a marked negative impact on quality of life as well as high hospitalization and mortality rates.[1] It is expected to become the third most common cause of death in the Western world by the year 2020.[2] Routinely used therapies in COPD focus on bronchial obstruction and do not or only marginally modify mortality risk.[1,3] Because COPD is also characterized by systemic inflammation,[1] other treatment options would be possible. Systemic inflammation in COPD promotes atherosclerotic disease progression[4] independent of age, smoking, or other cardiovascular risk factors.[5] Also, tobacco smoking is a major cause of COPD as well as of atherosclerosis. Therefore, patients with COPD are prone to develop cardiovascular diseases, which account for most deaths in these patients.[4,5]

See also pages 849 and 874

It has recently been emphasized that the differential diagnosis between chronic pulmonary and heart disease is difficult.[6] Ischemic heart disease and heart failure could be asymptomatic in patients with COPD when breathlessness, fatigue, and even chest pain on exertion are misinterpreted as COPD-related symptoms.[6] Indeed, recent studies showed high prevalence rates of heart failure in elderly patients with COPD, with most cases being unrecognized.[7,8]

Therapy with cardiovascular drugs, notably β-blockers, is known to improve the survival of patients within a large spectrum of cardiovascular diseases, including ischemic heart disease and heart failure.[9,10] β-Blockers could theoretically also exert beneficial effects in patients with COPD by tempering the sympathetic nervous system or by reducing the ischemic burden.[11] Meta-analyses have already shown that cardioselective β-blockers are well tol-

Author Affiliations: Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht (Drs Rutten, Hak, Grobbee, and Hoes and Mr Zuithoff), and Department of Epidemiology, University Medical Center Groningen, Groningen (Dr Hak), the Netherlands.

erated by patients with COPD,[12] even those with some reversibility (asthmatic component).[13] In patients with COPD, single-dose or long-term treatment with cardioselective β-blockers did not have a significant effect on forced expiratory volume in 1 second (FEV_1), β2-agonist response, inhaler use, or respiratory symptoms.[12] In patients with reactive airway disease, the use of cardioselective β-blockers was associated with a small decrease in FEV_1 and a similar small increase in β-agonist response with the first dose, both of which normalized with continued treatment.[13,14] The traditional dogma, however, states that β-blockers are contraindicated in COPD because of their presumed bronchoconstrictive properties and "competition" with β2-agonists[15]; therefore, many physicians avoid prescribing β-blockers in patients with COPD.[16]

There is evidence about the mortality-reducing potential of β-blocker use in certain subpopulations of patients with COPD and cardiovascular disease, ie, in patients post–myocardial infarction and in those undergoing major vascular surgery.[17,18] However, there is no clear evidence that β-blocker use increases the survival of patients with COPD without (overt) cardiovascular comorbidities. Only a single study showed that treatment with β-blockers had a nonsignificant tendency to reduce all-cause mortality in patients with COPD and hypertension.[19] We therefore wanted to assess whether long-term β-blocker use improves survival and reduces the risk of exacerbations in patients with COPD at large, including patients with COPD but without cardiovascular disease.

METHODS

SETTINGS AND PATIENTS

This cohort study was performed within the framework of the Utrecht General Practitioners (GPs) Network database, a network consisting of 35 collaborating GPs working in 23 practices in the vicinity of Utrecht, the Netherlands. Since 1992, GPs electronically enter all data related to daily patient contacts into a GP information system.[20] The information, which includes disease status, reasons for encounter, specialist letters, and medical prescriptions, is available for all patient encounters.[20] All diagnoses and drug prescriptions are coded according to the *International Classification of Primary Care, Second Edition* (*ICPC-2*), and the *Anatomical Therapeutic Chemical Classification* standard, respectively.[21] In December 2005, the network included approximately 60 000 patients, 20 362 of whom were 45 years or older.

The present study included all patients 45 years or older with an incident or prevalent diagnosis of COPD (*ICPC-2* code R91 [chronic bronchitis] or R95 [COPD or emphysema]) between January 1, 1995, and December, 31, 2005. The *ICPC-2* codes are based on symptoms (dyspnea, cough, or sputum production for at least 3 months a year for 2 consecutive years) and pulmonary rhonchi during these episodes and, in case of R95, preferably with spirometric evidence of pulmonary obstruction.[21] From a previous study, we know that in approximately 70% of cases the diagnosis of COPD conforms to the GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria.[22]

All-cause mortality and the first exacerbation of COPD within the study time frame were the outcomes of the study. Eligible patients were followed up until they died (study end point) or moved or until the end of the study period (December 31, 2005), whichever came first. Patients who experienced exacerbations of COPD remained eligible for the study outcome of death. Those who moved and thus left the care of the GP connected with the network during the study period were censored and contributed no person time or events beyond that time. An exacerbation of COPD was defined as a pulsed-dose prescription of prednisone or prednisolone during 7 to 10 days and/or a hospital admission for an exacerbation. The study was conducted in accordance with the Law for the Protection of Personal Data (in Dutch: *Wet Bescherming Persoonsgegevens*) and conformed to the Declaration of Helsinki.

DATA ANALYSIS

Cox proportional (CP) hazards regression analyses were used to calculate crude (unadjusted) and adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) for the risk of all-cause death and COPD exacerbation associated with the use of β-blockers as well as separately for selective and nonselective β-blockers. Adjusted HRs were calculated after correction for the following (potentially confounding) variables: age, sex, current and former smoking, history of cardiovascular disease (ie, angina pectoris, myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, atrial fibrillation, heart failure, peripheral arterial disease, or stroke), hypertension, diabetes mellitus, cardiovascular drug use other than β-blockers, pulmonary drug use, and referral to a pulmonologist.

Also, a propensity score (PS) technique was used as a method to balance covariates associated with β-blocker use between groups.[23] The PS was calculated as a continuous variable and was derived from a logistic regression model, with β-blocker use as the dichotomous dependent variable and the following covariates known from the literature to be associated with β-blocker prescription as independent variables: history of hypertension, angina pectoris, myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, atrial fibrillation, or heart failure. The adjusted HRs of β-blocker use were then calculated by including the continuous PS as the only covariate in the Cox analysis.[23] The logistic model to record the continuous PS with β-blocker use as the dichotomous dependent variable had an area under the receiver operating characteristic curve of 0.77 (95% CI, 0.75-0.80), indicating that the model adequately predicted β-blocker use.

To address the possibility of (residual) confounding by indication, we performed subgroup analyses, including patients with COPD but without overt cardiovascular disease, ie, without angina pectoris, myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, atrial fibrillation, heart failure, peripheral arterial disease, stroke, or diabetes, thus leaving hypertension as the main remaining indication for the prescription of β-blockers. Other subgroups that we studied separately consisted of patients with COPD (1) who used 2 or more pulmonary drugs, (2) who inhaled β-agonists, (3) who inhaled anticholinergic agents, and (4) who were referred to a pulmonologist; a fifth group comprised incident cases of COPD.

Because only 44 patients (2.0%) used a β-blocker as the single cardiovascular agent, we did not perform a separate analysis of this subgroup of patients. Interestingly, these 44 patients had much lower event rates than other subgroups. Only 3 patients (6.8%) died, and 6 (13.6%) had 1 or more exacerbations of COPD. Smoking status was missing in 34.1% of patients. As the exclusion of patients with a missing value (so-called complete case analysis) may lead to biased results and loss of power, we imputed missing values for smoking status by using a regression method with the addition of a random error term.[24] Imputation was based on the correlation between this missing variable and all other variables. As a check, we performed a separate reanalysis that was restricted to "full cases," ie, without

Table 1. Characteristics of 2230 Patients 45 Years or Older With a Diagnosis of Chronic Obstructive Pulmonary Disease According to β-Blocker Use

Characteristic	No. (%)			*P* Value
	All Patients (N=2230)	β-Blocker Use (n=665)	No β-Blocker Use (n=1565)	
Age, mean (SD), y[a]	64.8 (11.2)	64.7 (10.3)	64.8 (10.3)	.87
Male sex	1183 (53.0)	331 (49.8)	852 (54.4)	.04
Referral to a pulmonologist	575 (25.8)	151 (22.7)	424 (27.1)	.03
Current smokers[b]	545 (37.1)	166 (34.6)	379 (38.3)	.16
Former smokers[b]	723 (49.2)	245 (51.0)	478 (48.3)	.33
Never smokers[b]	201 (13.7)	69 (14.4)	132 (13.3)	.59
Cardiovascular risk factors				
Hypertension	875 (39.2)	444 (66.8)	431 (27.5)	<.001
Diabetes	372 (16.7)	160 (24.1)	212 (13.5)	<.001
Cardiovascular diseases				
Angina pectoris	363 (16.3)	217 (32.6)	146 (9.3)	<.001
Myocardial infarction	104 (4.7)	64 (9.6)	40 (2.6)	<.001
Ischemic heart disease[c]	439 (19.7)	255 (38.3)	184 (11.8)	<.001
Atrial fibrillation	222 (10.0)	125 (18.8)	97 (6.2)	<.001
Heart failure	546 (24.5)	213 (32.0)	333 (21.3)	<.001
Stroke	155 (7.0)	60 (9.0)	95 (6.1)	.01
Peripheral arterial disease	162 (7.3)	75 (11.3)	87 (5.6)	<.001
Cardiovascular drug use				
β-Blockers	665 (29.8)	NA	NA	NA
Cardioselective	NA	545 (24.4)	NA	NA
Nonselective	NA	193 (8.7)	NA	NA
Angiotensin-converting enzyme inhibitors	667 (29.9)	331 (49.8)	336 (21.5)	<.001
Angiotensin receptor blockers	191 (8.6)	110 (16.5)	81 (5.2)	<.001
Aldosterone antagonists[d]	188 (8.4)	83 (12.5)	105 (6.7)	<.001
Acetylsalicylic acid or clopidogrel	374 (16.8)	198 (29.8)	176 (11.2)	<.001
Statins	393 (17.6)	222 (33.4)	171 (10.9)	<.001
Thiazide diuretics	413 (18.5)	209 (31.4)	203 (13.0)	<.001
Loop diuretics	850 (38.1)	325 (48.9)	525 (33.5)	<.001
Nitrates	457 (20.5)	246 (37.0)	211 (13.5)	<.001
Calcium channel blockers	421 (18.9)	227 (34.1)	194 (12.4)	<.001
Digoxin	244 (10.9)	107 (16.1)	137 (8.8)	<.001
Vitamin K antagonists	437 (19.6)	208 (31.3)	229 (14.6)	<.001
Pulmonary drug use				
Inhaled β_2-sympathicomimetics	1288 (57.8)	349 (52.5)	939 (60.0)	.001
Short-acting	1056 (47.4)	277 (41.7)	779 (49.8)	<.001
Long-acting	621 (27.8)	162 (24.4)	459 (29.3)	.02
Anticholinergic inhalers	1357 (60.9)	432 (65.0)	925 (59.1)	.01
Inhalation corticosteroids	1354 (60.7)	399 (60.0)	955 (61.0)	.65
Xanthine derivates	154 (6.9)	32 (4.8)	122 (7.8)	.01

Abbreviation: NA, not applicable.
[a] At study entry.
[b] Percentages were calculated for 1469 participants because smoking status was missing in 761 persons (34.1%).
[c] Ischemic heart disease is a composite variable consisting of patients with angina pectoris, prior myocardial infarction, coronary artery bypass grafting, or percutaneous coronary intervention.
[d] Aldosterone antagonists are spironolactone and eplerenone.

imputation of missing smoking status, with similar results on the Cox regression analyses, although with broader CIs, as a result. As a second check, we performed sensitivity analyses in which all patients with missing smoking status were defined first as smokers (former and current) and second as nonsmokers, again showing similar results on the Cox regression analyses. All analyses were performed using SPSS Windows version 15.0 (SPSS Inc, Chicago, Illinois).

RESULTS

A total of 2230 patients 45 years and older with a diagnosis of COPD were included in the study. Of the 2230 patients, 560 (25%) had prevalent COPD at the start of the study and 1670 (75%) developed COPD during the follow-up period (incident COPD). The mean (SD) age of the patients at the start of the study period was 64.8 (11.2) years, and 53% of the patients were male. In total, 686 patients (30.8%) died: 27.2% of those who used a β-blocker compared with 32.3% of those who did not use a β-blocker (P=.02). One thousand fifty-five patients (47.3%) had at least 1 exacerbation of COPD during the mean (SD) follow-up period of 7.2 (2.8) years: 42.7% of those who used a β-blocker and 49.3% of those who did not use a β-blocker (P=.005). Patient characteristics according to β-blocker use are presented in **Table 1**. In total, 44.9% of the patients with COPD had cardiovas-

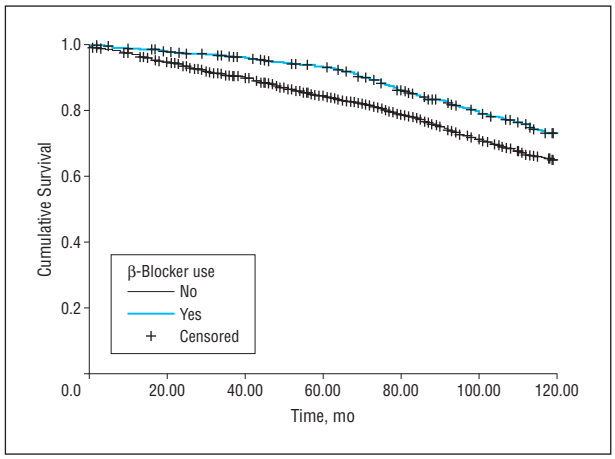

Figure 1. Cumulative survival of patients with chronic obstructive pulmonary disease according to β-blocker use.

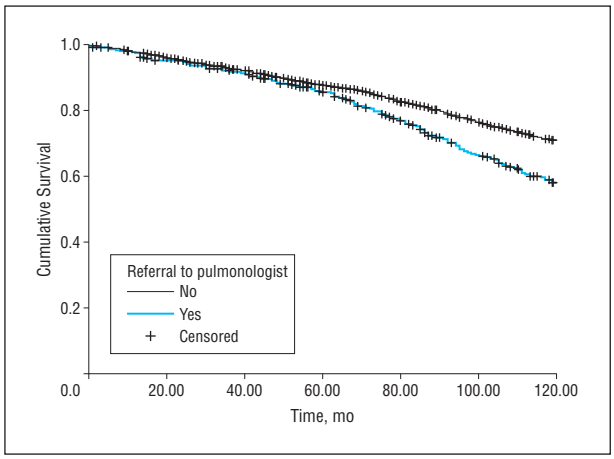

Figure 2. Cumulative survival of patients with chronic obstructive pulmonary disease according to referral to a pulmonologist.

Table 2. Crude and Adjusted Hazard Ratios (HRs) for Mortality According to β-Blocker Use in 2230 Patients With a Diagnosis of Chronic Obstructive Pulmonary Disease[a]

Variable	HR (95% Confidence Interval)		
	Any β-Blocker	Cardioselective β-Blocker	Nonselective β-Blocker
Unadjusted (crude)	0.70 (0.59-0.84)	0.69 (0.57-0.83)	0.80 (0.61-1.06)
Covariates included in the Cox model to calculate adjusted HRs +			
Age	0.66 (0.56-0.79)	0.64 (0.54-0.78)	0.80 (0.61-1.05)
Sex	0.69 (0.58-0.82)	0.66 (0.55-0.80)	0.84 (0.63-1.11)
Current or former smoker	0.69 (0.58-0.81)	0.66 (0.55-0.79)	0.83 (0.63-1.10)
Diabetes, hypertension, cardiovascular diseases	0.65 (0.54-0.79)	0.64 (0.52-0.79)	0.77 (0.57-1.03)
Cardiovascular drugs other than β-blocker	0.67 (0.55-0.81)	0.64 (0.52-0.79)	0.82 (0.61-1.10)
Pulmonary drugs	0.67 (0.55-0.82)	0.65 (0.53-0.80)	0.82 (0.61-1.10)
Referral to a pulmonologist	0.68 (0.56-0.83)	0.67 (0.55-0.83)	0.82 (0.61-1.10)
Adjusted with propensity score[b]	0.64 (0.52-0.77)	0.63 (0.51-0.77)	0.80 (0.60-1.05)

[a] Adjusted HRs based on the Cox proportional hazards model were calculated step by step after adjustment for age, sex, current or former smoking, diabetes, hypertension, cardiovascular diseases, cardiovascular drugs other than the one under study, use of pulmonary inhalation drugs, and referral to a pulmonologist. Cardiovascular drugs include β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, digoxin, loop and thiazide diuretics, nitrates, aspirin, vitamin K antagonists, and calcium channel blockers. Pulmonary drugs include inhalers of β_2-agonists, anticholinergic agents, corticosteroids, and oral xanthine derivates.

[b] Adjusted HRs of β-blocker use are conditional on the propensity score (based on covariates related to prescription of β-blockers).

cular comorbidities. The number of patients with either cardiovascular disease or hypertension or diabetes was even higher (66.3%). This last group had significantly higher mortality rates than those without these diseases or cardiovascular risk factors (35.5% vs 21.4%; $P < .001$). As a consequence of these comorbidities, the number of cardiovascular drug prescriptions was high. As many as 665 patients (29.8%) were prescribed β-blockers, mainly cardioselective ones (24.4%). Kaplan-Meier curves showed that patients who used β-blockers had a higher survival rate than nonusers (**Figure 1**), while patients with COPD who were referred to a pulmonologist had a lower survival rate than those who were not referred during the follow-up period (**Figure 2**).

ALL-CAUSE MORTALITY

The crude and adjusted HRs based on the multivariable CP hazard model for β-blocker use were 0.70 (95% CI, 0.59-0.84) and 0.68 (95% CI, 0.56-0.83), respectively. The adjusted HR conditional on the PS was 0.64 (95% CI, 0.52-0.77). For cardioselective β-blockers, the adjusted HRs (CP and PS) were 0.67 (95% CI, 0.55-0.83) and 0.63 (95% CI, 0.51-0.77). For nonselective β-blockers, the adjusted HRs (CP and PS) were 0.82 (95% CI, 0.61-1.10) and 0.80 (95% CI, 0.60-1.05), respectively (**Table 2**).

ALL-CAUSE MORTALITY IN SUBGROUPS

In the subgroup of patients without overt cardiovascular disease (n = 1229), 239 patients (19.4%) used β-blockers, and in total 241 patients (19.6%) died. The crude HR and the adjusted HRs (CP and PS) for any β-blocker use in this subgroup were 0.60 (95% CI, 0.41-0.87), 0.67 (95% CI, 0.45-0.99), and 0.68 (95% CI, 0.46-1.02), respectively (**Table 3**).

Other subgroup analyses showed similar results, with the exception of patients referred to the pulmonologist (Table 3). This last subgroup showed a lower and nonsignificant reduction of mortality, with crude HR and ad-

Table 3. Crude and Adjusted Hazard Ratios (HRs) for Mortality According to β-Blocker Use in Subgroups of Patients With a Diagnosis of Chronic Obstructive Pulmonary Disease (COPD)

Variable	HR (95% Confidence Interval)
No overt cardiovascular disease (n=1229); 241(19.6%) died	Any β-blocker (n=239)
Unadjusted (crude)	0.60 (0.41-0.87)
Adjusted with Cox[a]	0.67 (0.45-0.99)
Adjusted with propensity score[b]	0.68 (0.46-1.02)
Patients who used 2 or more pulmonary drugs (n=1419); 442 (31.1%) died	Any β-blocker (n=417)
Unadjusted (crude)	0.66 (0.53-0.82)
Adjusted with Cox[a]	0.62 (0.48-0.80)
Adjusted with propensity score[b]	0.60 (0.49-0.74)
Patients who used β_2-sympathicomimetics (n=1288); 384 (29.8%) died	Any β-blocker (n=349)
Unadjusted (crude)	0.66 (0.52-0.83)
Adjusted with Cox[a]	0.64 (0.49-0.85)
Adjusted with propensity score[b]	0.60 (0.46-0.79)
Patients who inhaled anticholinergic agents (n=1357); 463 (34.1%) died	Any β-blocker (n=432)
Unadjusted (crude)	0.68 (0.56-0.84)
Adjusted with Cox[a]	0.68 (0.53-0.87)
Adjusted with propensity score[b]	0.60 (0.48-0.76)
Incident cases of COPD (n=1670); 472 (28.3%) died	Any β-blocker (n=530)
Unadjusted (crude)	0.73 (0.59-0.89)
Adjusted with Cox[a]	0.73 (0.57-0.92)
Adjusted with propensity score[b]	0.63 (0.50-0.79)
Patients who were referred to a pulmonologist (n=575); 233 (40.5%) died	Any β-blocker (n=151)
Unadjusted (crude)	0.80 (0.59-1.08)
Adjusted with Cox[a]	0.72 (0.51-1.03)
Adjusted with propensity score[b]	0.81 (0.58-1.13)

[a] Adjusted Cox HRs of β-blocker use were calculated step by step after adjustment for age, sex, current or former smoking, cardiovascular risk factors, cardiovascular diseases, cardiovascular drugs other than the one under study, use of pulmonary inhalation drugs, and referral to a pulmonologist.

[b] Adjusted HRs of β-blocker use are conditional on the propensity score (based on covariates related to prescription of β-blockers).

justed HRs (CP and PS) for any β-blocker use of 0.80 (95% CI, 0.59-1.08), 0.72 (95% CI, 0.51-1.03), and 0.81 (95% CI, 0.58-1.13), respectively (Table 3).

Of the 1670 patients with incident COPD, 530 used a β-blocker: 191 patients already used β-blockers and continued the use after the diagnosis; 84 patients stopped using β-blockers at the time of diagnosis; and 255 patients started β-blocker use after the diagnosis of COPD. Separate analyses of these 3 subgroups of patients with incident COPD showed that those who discontinued β-blocker use had the highest HRs for mortality, with crude and adjusted HRs (CP and PS) of 0.71 (95% CI, 0.46-1.11), 0.89 (95% CI, 0.56-1.42), and 0.75 (95% CI, 0.47-1.19), respectively.

EXACERBATIONS OF COPD NECESSITATING PULSED-DOSE PREDNISONE OR PREDNISOLONE

The adjusted HRs (CP and PS) of an exacerbation for any β-blocker use were 0.71 (95% CI, 0.60-0.83) and 0.64 (95% CI, 0.55-0.75), respectively, which were in the same range of the effect seen on survival (**Table 4**). Cardioselective and nonselective β-blockers did not substantially differ in their effects.

EXACERBATIONS OF COPD IN SUBGROUPS

In the subgroup of patients without overt cardiovascular disease, 42.3% experienced at least 1 exacerbation of COPD during the follow-up. The crude HR and adjusted HRs (CP and PS) for any β-blocker use in this subgroup were 0.66 (95% CI, 0.53-0.84), 0.66 (95% CI, 0.52-0.86), and 0.68 (95% CI, 0.46-1.02), respectively (**Table 5**). Other subgroup analyses showed similar results, including the subgroup of patients who were referred to a pulmonologist (Table 5).

COMMENT

To our knowledge, this is the first observational study that shows that long-term treatment with β-blockers may improve survival and reduce the risk of an exacerbation of COPD in the broad spectrum of patients with a diagnosis of COPD, including those who have COPD with but, importantly, also without overt cardiovascular comorbidities. Cardioselective β-blockers have larger beneficial effects on mortality than nonselective ones but similar effects on the risk of exacerbation of COPD. Whether β-blockers can also cause beneficial pulmonary activity and therefore are truly "cardiopulmonary" drugs remains to be proved. Patients without (overt) cardiovascular comorbidities in our study still had hypertension as the reason for β-blocker use, and β-blockers are well known to reduce cardiovascular mortality in the treatment of hypertension. Importantly, however, the reduction in risk of exacerbation of COPD by β-blockers cannot easily be explained by cardiovascular effects alone. The association with survival also remained in the very small group of 44 patients who used β-blockers as single-agent cardiovascular therapy, suggesting that β-blockers offer a class-specific effect, independent of other cardiovascular drugs.

Previous observational studies in patients with COPD have already shown the beneficial effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and statins on all-cause mortality.[25,26] We were unable to reproduce these beneficial effects for angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in our study (adjusted Cox HR, 1.01; 95% CI, 0.84-1.21). For statins, we could detect a nonsignificant beneficial trend for survival (adjusted Cox HR, 0.83; 95% CI, 0.65-1.08) (data not shown). An observational study with β-blockers as single-agent therapy in patients with hypertension and (partly self-reported) COPD showed that β-blockers had a tendency to reduce all-cause mortality compared with other cardiovascular drugs.[19] Importantly, in this last study, calcium channel blockers and diuretics did not have mortality-reducing capacities in these patients with COPD.[19,26] Recently, a small retrospective observational study suggested that patients who were using β-blockers at the time of hospitalization for an acute exacerbation of COPD had lower in-hospital mortality.[27] Also, in this last study, calcium channel blockers did not prove to have mortality-reducing capacities.

Table 4. Crude and Adjusted Hazard Ratios (HRs) for Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) According to β-Blocker Use in 2230 Patients With a Diagnosis of COPD[a]

Variable	HR (95% Confidence Interval)		
	Any β-Blocker	Cardioselective β-Blocker	Nonselective β-Blocker
Unadjusted (crude)	0.73 (0.63-0.83)	0.75 (0.65-0.87)	0.72 (0.57-0.90)
Covariates included in the Cox model to calculate adjusted HRs +			
Age	0.71 (0.62-0.82)	0.74 (0.64-0.86)	0.71 (0.56-0.89)
Sex	0.71 (0.62-0.81)	0.74 (0.64-0.85)	0.70 (0.56-0.89)
Current or former smoker	0.70 (0.61-0.80)	0.73 (0.63-0.84)	0.71 (0.56-0.89)
Diabetes, hypertension, cardiovascular diseases	0.63 (0.54-0.74)	0.68 (0.58-0.80)	0.66 (0.52-0.84)
Cardiovascular drugs other than β-blocker	0.58 (0.50-0.68)	0.64 (0.54-0.75)	0.66 (0.52-0.84)
Pulmonary drugs	0.67 (0.57-0.79)	0.72 (0.61-0.85)	0.72 (0.56-0.91)
Referral to a pulmonologist	0.71 (0.60-0.83)	0.78 (0.66-0.92)	0.74 (0.58-0.94)
Adjusted with propensity score[b]	0.64 (0.55-0.75)	0.68 (0.58-0.80)	0.70 (0.56-0.89)

[a] Adjusted HRs based on the Cox proportional hazards model were calculated step by step after adjustment for age, sex, current or former smoking, diabetes, hypertension, cardiovascular diseases, cardiovascular drugs other than the one under study, use of pulmonary inhalation drugs, and referral to a pulmonologist. Cardiovascular drugs include β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, digoxin, loop and thiazide diuretics, nitrates, aspirin, vitamin K antagonists, and calcium channel blockers. Pulmonary drugs include inhalers of β_2-agonists, anticholinergic agents, corticosteroids, and oral xanthine derivates.

[b] Adjusted HRs of β-blocker use are conditional on the propensity score (based on covariates related to prescription of β-blockers).

In our study, however, calcium channel blockers had a significant beneficial effect on all-cause mortality, with an adjusted Cox HR of 0.77 (95% CI, 0.62-0.96), while diuretics had an adjusted Cox HR of 1.27 (95% CI, 1.04-1.57) (data not shown).

The beneficial effects of the use of multiple cardiovascular drugs in patients with COPD suggests that treatment of (concealed) concurrent cardiovascular disease could play a role.[26] Previous studies have shown that the beneficial effect of β-blockade on mortality among patients after myocardial infarction was similar for those with and without COPD and that the use of β-blockers improved survival in patients with COPD who had concurrent hypertension or signs of atherosclerosis.[18,19] These results, and the fact that our study showed that more than half of the patients with COPD had cardiovascular risk factors or overt cardiovascular diseases, similar to previous studies,[8,25] should urge physicians to be alert to detect (early stages of) cardiovascular diseases in these patients. In every patient with COPD, history taking should include questions about chest discomfort that is suggestive of angina pectoris, and physical examination should include an investigation of the heart and measurements of blood pressure and pulse rate. In case of doubt, we recommend additional investigations such as B-type natriuretic peptide measurements, (exercise) electrocardiography, and, if the results of one of these tests are abnormal, echocardiography.[22] Interestingly, the association of β-blocker use with all-cause mortality and risk of exacerbation of COPD also remained in patients who were taking 2 or more pulmonary drugs or who were using inhaled β_2 sympathicomimetics or anticholinergic agents. Therefore, inhaled pulmonary medication seems not to interfere with the results of β-blocker use.

β-Blockers are known to temper the sympathetic nervous system, including the reduction of the heart rate; therefore, the negative systemic effects in the disease progression of COPD could be diminished.[11] Clinical trial data already suggest that heart rate reduction itself is an important mechanism of the benefit of β-blockers, and large epidemiological studies have shown that resting heart rate was an independent predictor of all-cause mortality in individuals with and without cardiovascular disease.[28]

The beneficial effects of β-blocker use on the survival in patients who use inhalation of β_2-sympathicomimetics may seem unexpected. However, animal models have already shown that β-blockers can upregulate β_2-receptors in the lung and thus even improve the bronchodilator responsiveness and effectiveness of inhaled β_2-sympathicomimetics,[29] an effect that at first glance, and at least to some physicians, seems a contraintuitive pathway by which β-blockers could exhibit beneficial effects.[15] Interestingly, previous studies have also shown that β-agonists can downregulate β_2-receptors in asthma and COPD.[30] Moreover, there are concerns that the use of β-agonists could increase all-cause mortality.[31] In our study, the subgroup of patients who used inhaled β-agonists had similar effects of concomitant β-blocker use on mortality and risk of exacerbation of COPD as other subgroups of patients with COPD (Table 3 and Table 5).

LIMITATIONS

In our primary care cohort, some of the patients may have been misclassified as having COPD, and complaints such as breathlessness and fatigue could have been caused by concealed ischemic heart disease or heart failure,[8,25] diseases in which the mortality-reducing effects of β-blockers are well established.[9] It is possible that we could not completely correct for confounding by indication in that more severely ill patients were more likely to receive cardiovascular drugs, including β-blockers. Importantly, however, this confounding by indication would lead to underestimation of a beneficial treatment effect.[32] On the contrary, "healthy user bias" does not seem to play an important role because the effect estimates in patients without overt cardiovascular disease were similar to those in the total population. Another limitation of our study is that

Table 5. Crude and Adjusted Hazard Ratios (HRs) for Exacerbations of Chronic Obstructive Pulmonary Disease (COPD) According to β-Blocker Use in Subgroups of Patients With a Diagnosis of COPD

Variable	HR (95% Confidence Interval)
No overt cardiovascular disease (n=1229); 520 (42.3%) with an exacerbation of COPD	Any β-blocker (n=239)
Unadjusted (crude)	0.66 (0.53-0.84)
Adjusted with Cox[a]	0.66 (0.52-0.86)
Adjusted with propensity score[b]	0.68 (0.46-1.02)
Patients who used 2 or more pulmonary drugs (n=1419); 880 (62.0%) with an exacerbation of COPD	Any β-blocker (n=417)
Unadjusted (crude)	0.76 (0.65-0.88)
Adjusted with Cox[a]	0.72 (0.60-0.86)
Adjusted with propensity score[b]	0.69 (0.58-0.82)
Patients who used β_2-sympathicomimetics (n=1288); 805 (62.5%) with an exacerbation of COPD	Any β-blocker (n=349)
Unadjusted (crude)	0.78 (0.66-0.91)
Adjusted with Cox[a]	0.71 (0.59-0.86)
Adjusted with propensity score[b]	0.70 (0.59-0.84)
Patients who inhaled anticholinergic agents (n=1357); 788 (58.1%) with an exacerbation of COPD	Any β-blocker (n=432)
Unadjusted (crude)	0.73 (0.62-0.85)
Adjusted with Cox[a]	0.71 (0.59-0.85)
Adjusted with propensity score[b]	0.65 (0.54-0.78)
Incident cases of COPD (n=1670); 774 (46.3%) with an exacerbation of COPD	Any β-blocker (n=530)
Unadjusted (crude)	0.77 (0.66-0.90)
Adjusted with Cox[a]	0.73 (0.60-0.88)
Adjusted with propensity score[b]	0.66 (0.56-0.79)
Patients who were referred to a pulmonologist (n=575); 414 (72.0%) with an exacerbation of COPD	Any β-blocker (n=151)
Unadjusted (crude)	0.70 (0.56-0.88)
Adjusted with Cox[a]	0.66 (0.50-0.86)
Adjusted with propensity score[b]	0.67 (0.52-0.87)

[a] Adjusted Cox HRs of β-blocker use, step by step after adjustment for age, sex, current or former smoking, cardiovascular risk factors, cardiovascular diseases, cardiovascular drugs other than the one under study, use of pulmonary inhalation drugs, and referral to a pulmonologist.

[b] Adjusted HRs of β-blocker use are conditional on the propensity score (based on covariates related to prescription of β-blockers).

GPs do not always use spirometry to classify patients with COPD. Another study performed by our group in the same region in the Netherlands showed that 60% of the patients who are diagnosed as having COPD by their GP (*ICPC-2* code R91 or R95) indeed have COPD according to the GOLD criteria, with a postdilatory FEV_1 and forced vital capacity ratio of less than 70%.[22] However, an unconfirmed (clinical) diagnosis of COPD is not a phenomenon that is exclusively seen in primary care; it is even rather common in patients who are being treated by pulmonologists.[25,33] As already mentioned, misclassified patients with COPD could have concealed cardiovascular disease as the reason for their complaints. Although this phenomenon certainly could have played a role in our study, it is of interest that β-blocker use was still associated with an independent beneficial effect on mortality in those without cardiovascular disease. Therefore, residual confounding caused by unobserved covariates cannot be completely ruled out.[32] Importantly, the HRs of β-blocker use in our study changed in the anticipated direction in the Cox analysis when the different confounders were included one at a time. This means that potential unobserved confounders should be stronger than the observed ones that were put in our model to change the size of the effect, and it is unlikely that such residual confounding exists.[32]

Although the smoking status was missing in many cases, complete case analysis as well as sensitivity analysis revealed that this had no impact on the effect estimates. Smoking status therefore seems not to be a confounder. Moreover, it was not related to β-blocker use (Table 1).[32]

STRENGTHS

We included a large representative sample of patients with COPD with various cardiovascular risk profiles and a long follow-up period. In our nonrandomized study, we were able to correct for many potential confounders, and adjusted HRs were similar after Cox regression analysis and the PS method for β-blocker use. Moreover, all patients with COPD were included in our database, including those who were (co-)treated by a pulmonologist, because all individuals, except nursing residents, are registered with a general practice in the Netherlands.

CONCLUSIONS

The results of our study suggest that the use of β-blockers may reduce mortality as well as the risk of exacerbations of COPD in a broad spectrum of patients with COPD with concurrent hypertension or cardiovascular disease. A meta-analysis of randomized trials has already shown that (cardioselective) β-blockers are well tolerated by patients with COPD.[13] The time has come to confirm these results in a randomized controlled trial.

Accepted for Publication: November 16, 2009.
Correspondence: Frans H. Rutten, MD, PhD, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, PO Box 85060, Stratenum 6.101, 3508 AB Utrecht, the Netherlands (F.H.Rutten@umcutrecht.nl)
Author Contributions: Dr Rutten had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Rutten, Grobbee, and Hoes. *Acquisition of data:* Rutten and Zuithoff. *Analysis and interpretation of data:* Rutten, Zuithoff, Hak, Grobbee, and Hoes. *Drafting of the manuscript:* Rutten. *Critical revision of the manuscript for important intellectual content:* Zuithoff, Hak, Grobbee, and Hoes. *Statistical analysis:* Rutten, Zuithoff, Hak, Grobbee, and Hoes. *Administrative, technical, and material support:* Zuithoff and Grobbee. *Study supervision:* Grobbee and Hoes.
Financial Disclosure: None reported.
Additional Contributions: We thank the participating patients and the GPs of the Utrecht General Practitioners Network.

REFERENCES

1. Rabe KF, Hurd S, Anzueto A, et al; Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2007;176(6):532-555.
2. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet*. 1997;349(9064):1498-1504.
3. Calverley PM, Anderson JA, Celli B, et al; TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356(8):775-789.
4. Sin DD, Man SF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? the potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation*. 2003;107(11):1514-1519.
5. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ*. 1996;313(7059):711-716.
6. Rutten FH, Cramer MJ, Lammers JW, Grobbee DE, Hoes AW. Heart failure and chronic obstructive pulmonary disease: an ignored combination? *Eur J Heart Fail*. 2006;8(7):706-711.
7. McCullough PA, Hollander JE, Nowak RM, et al; BNP Multinational Study Investigators. Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department. *Acad Emerg Med*. 2003;10(3):198-204.
8. Rutten FH, Cramer MJ, Grobbee DE, et al. Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. *Eur Heart J*. 2005; 26(18):1887-1894.
9. Smith SC Jr, Allen J, Blair SN, et al; AHA/ACC; National Heart, Lung, and Blood Institute. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation*. 2006;113(19):2363-2372.
10. Hunt SA, Abraham WT, Chin MH, et al; American College of Cardiology Foundation; American Heart Association. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the International Society for Heart and Lung Transplantation. *J Am Coll Cardiol*. 2009;53 (15):e1-e90.
11. Andreas S, Anker SD, Scanlon PD, Somers VK. Neurohumoral activation as a link to systemic manifestations of chronic lung disease. *Chest*. 2005;128(5):3618-3624.
12. Salpeter SS, Ormiston T, Salpeter E, Poole P, Cates C. Cardioselective beta-blockers for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2002;(2):CD003566.
13. Salpeter SR, Ormiston TM, Salpeter EE. Cardioselective beta-blockers in patients with reactive airway disease: a meta-analysis. *Ann Intern Med*. 2002;137(9):715-725.
14. Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for reversible airway disease. *Cochrane Database Syst Rev*. 2002;(4):CD002992.
15. Ling Y, Saleem W, Shee CD. Concomitant use of beta-blockers and beta2-agonists. *Eur Respir J*. 2008;31(4):905-906.
16. Egred M, Shaw S, Mohammad B, Waitt P, Rodrigues E. Under-use of beta-blockers in patients with ischaemic heart disease and concomitant chronic obstructive pulmonary disease. *QJM*. 2005;98(7):493-497.
17. Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. *N Engl J Med*. 1998; 339(8):489-497.
18. van Gestel YR, Hoeks SE, Sin DD, et al. Impact of cardioselective beta-blockers on mortality in patients with chronic obstructive pulmonary disease and atherosclerosis. *Am J Respir Crit Care Med*. 2008;178(7):695-700.
19. Au DH, Bryson CL, Fan VS, et al. Beta-blockers as single-agent therapy for hypertension and the risk of mortality among patients with chronic obstructive pulmonary disease. *Am J Med*. 2004;117(12):925-931.
20. van der Lei J, Duisterhout JS, Westerhof HP, et al. The introduction of computer-based patient records in the Netherlands. *Ann Intern Med*. 1993;119(10):1036-1041.
21. ICPC-2. *International Classification of Primary Care*. 2nd ed. Oxford, England: Oxford University Press; 1998.
22. Rutten FH, Moons KG, Cramer MJ, et al. Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. *BMJ*. 2005;331(7529):1379.
23. Martens EP, Pestman WR, de Boer A, Belitser SV, Klungel OH. Systematic differences in treatment effect estimates between propensity score methods and logistic regression. *Int J Epidemiol*. 2008;37(5):1142-1147.
24. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. *Am J Epidemiol*. 1995;142(12):1255-1264.
25. Søyseth V, Brekke PH, Smith P, Omland T. Statin use is associated with reduced mortality in COPD. *Eur Respir J*. 2007;29(2):279-283.
26. Mancini GB, Etminan M, Zhang B, Levesque LE, FitzGerald JM, Brophy JM. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. *J Am Coll Cardiol*. 2006;47(12):2554-2560.
27. Dransfield MT, Rowe SM, Johnson JE, Bailey WC, Gerald LB. Use of beta blockers and the risk of death in hospitalised patients with acute exacerbations of COPD. *Thorax*. 2008;63(4):301-305.
28. Fox K, Borer JS, Camm AJ, et al; Heart Rate Working Group. Resting heart rate in cardiovascular disease. *J Am Coll Cardiol*. 2007;50(9):823-830.
29. Lin R, Peng H, Nguyen LP, et al. Changes in beta 2-adrenoceptor and other signaling proteins produced by chronic administration of "beta-blockers" in a murine asthma model. *Pulm Pharmacol Ther*. 2008;21(1):115-124.
30. Johnston SL, Edwards MR. Mechanisms of adverse effects of {beta}-agonists in asthma. *Thorax*. 2009;64(9):739-741.
31. Benedict CR, Shelton B, Johnstone DE, et al. Prognostic significance of plasma norepinephrine in patients with asymptomatic left ventricular dysfunction: SOLVD Investigators. *Circulation*. 1996;94(4):690-697.
32. Groenwold RH, Hak E, Hoes AW. Quantitative assessment of unobserved confounding is mandatory in nonrandomized intervention studies. *J Clin Epidemiol*. 2009;62(1):22-28.
33. Damarla M, Celli BR, Mullerova HX, Pinto-Plata VM. Discrepancy in the use of confirmatory tests in patients hospitalized with the diagnosis of chronic obstructive pulmonary disease or congestive heart failure. *Respir Care*. 2006;51(10):1120-1124.